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RAPID COMMUNICATION

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Aspirin and tension-type headache

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Abstract Acetylsalicylic acid (ASA, Aspirin) is among the most used drugs worldwide. At present, Aspirin represents a quite versatile drug employed in the control of pain symptomatology and in situations such as prevention of both ischaemic stroke and cardiovascular events. Aspirin causes inhibition of prostaglandin (PG) synthesis by inactivation of the cyclooxygenase (COX) enzyme. ASA constitutes the focus of new researches explaining more widely Aspirin's control of inflammation. The induction of the endogenous epimers lipoxins (Aspirin-triggered 15-epi-lipoxins, ATLs) represents

one of the most recent achievements. This particular feature of Aspirin is not shared by other NSAIDs. ASA is well known as a headache medication, figuring as a possible treatment choice in tension-type headache but also in acute migraine attacks.

Furthermore, a new Aspirin formulation with a greater rapidity of action has been introduced. In conclusion, little information exists on the subject and more studies are required.

Keywords Aspirin • ASA • Tension-type headache • Acute treatment

Introduction

Acetylsalicylic acid (ASA, Aspirin) is among the most used drugs worldwide. Although Aspirin is recognised as anti-inflammatory, analgesic and antipyretic, it is presently applied in several other clinical situations. Aspirin's low dosage (75–100 mg) is by now consolidated for secondary prevention of both ischaemic stroke and cardiovascular events. In the acute phase, higher dosages (>300 mg) are employed [1–3]. Besides, a possible role in the incidence reduction of colon, lung and breast cancer and even of Alzheimer's disease has been suggested [4–7].

The history of this substance dates back to the earliest times, at least to 2000 years ago. In the fifth century B.C., Hippocrates described the properties of a juice extracted from the cortex of the willow tree (*Salix alba*), which was able to treat pain and fever.

In 1826 two Italian chemists, Fontana and Brugnatelli, extracted the active principle from the willow and called it salicin. They were the first scientists who isolated the active ingredient, even though it was in a very impure form [8].

From 1859 onwards, Kolbe and his colleagues developed a process in which salicylic acid was synthetically obtained from salicin [9]. The Kolbe process consists of a chemical reaction of carboxylation that adds a phenolate to carbon dioxide of the salicylate molecular structure in

order to form salicylic acid through treatment with sulphuric acid. This product is toxic in high dosages *per os* and hence less tolerable.

In 1897 Felix Hoffman determined a stable and more tolerable form by combining acetylating salicylic acid with acetic acid, in this way obtaining ASA. Hoffman was motivated in his studies by his wish to treat his father's arthritis without producing stomach irritation, which drugs at that time caused, including salicylic acid.

In 1899 ASA was registered under the trademark Aspirin [10]. More than 70 years later, as Aspirin already represented the most used analgesic, antipyretic and anti-inflammatory substance in the world, Vane and his group discovered the mechanism of the action of Aspirin-like drugs [11]. Vane's research on Aspirin-like drugs gained him the Nobel Prize for Medicine in 1982.

Mechanism of action

Aspirin causes the irreversible inhibition of cyclooxygenase activity (COX), defined also as endoperoxide H synthase-1, by acetylation of a specific serine at the active site of the enzyme [12]. COX activity produces the formation of important mediators called prostanoids including prostaglandin, prostacyclin and thromboxane. The process occurs via selective acetylation of a hydroxyl group of a serine residue (Ser 530), located 70 amino acids from the C terminus protein [13]. The inhibition of prostaglandin (PG) formation is caused by the preclusion of arachidonic acid (AA) binding at this site [14]. COX converts AA (a polyunsaturated fatty acid present in the membranes phospholipids of the cells) to prostaglandin G₂ (PGG₂), which becomes metabolised by specific synthases, or not enzymatically into individual eicosanoids.

At present, we know three different COX isoforms. COX-1 is the constitutive isoform involving physiological processes such as gastric mucosa protection, platelet aggregation and kidney function [15]. COX-2 is induced by various stimuli such as mitogens, growth factors, cancer promoters and lipopolysaccharide, and constitutes the principal cause of PG synthesis during inflammatory reactions [16]. COX-2 was originally considered exclusively an "inducible" isoform, but it has proved to be constitutively expressed in several tissues including CNS, kidney and megakaryocytes [17–19].

COX-3 is a COX-1 variant, inhibited by acetaminophen and other analgesics/antipyretic drugs. COX-3, described as two smaller COX-1-derived proteins (partial COX-1 or PCOX-1 proteins), is produced by the COX-1 gene but with retention of intron 1 preventing translation and nuclear export of mRNA [20]. After Vane's discovery,

several studies added new explanations on Aspirin's inflammation control.

PG inhibition constitutes Aspirin's principal mechanism of action, as a result of COX acetylation. However, COX-2 acetylated isoform is not really inhibited but is still active because of a larger active site and as a consequence of an unusual L-shaped binding of AA within the COX-2 substrate channel [21]. In fact, this enzyme redirects the catalytic activity from intermediate generation in a pathway of PGs and thromboxane (TX) to conversion of AA to 15(*R*)-hydroxyeicosatetraenoic (15*R*-HETE). Subsequently, 15*R*-HETE is rapidly metabolised by leukocyte 5-lipoxygenase to generate 15 epi-LXA₄ or 15 epi-LXB₄ [22]. These epimers of lipoxin A₄ are named Aspirin-triggered 15-epi-lipoxin A₄ and B₄ (ATLs).

Therefore, Aspirin has a direct impact on lipoxygenase interaction products (lipoxins, LX). Both LX circuit and Aspirin-triggered biosynthesis of endogenous epimers of LX play an important role as mediators of key events in endogenous anti-inflammation and resolution. Differently from other NSAIDs, this new mechanism of action represents an exclusive property of Aspirin [23]. This suggests a main role not only in the inhibition of pro-inflammatory mediators, but also in the induction of endogenous anti-inflammatory factors [24].

15-epi-lipoxin A₄ production in humans also depends on a low daily Aspirin dosage (81 mg) exerting an anti-inflammatory action through local production of 15-LXs. This has been documented in a randomised human trial of healthy volunteers conducted by Chiang et al. [25].

Furthermore, ATLs elicit nitric oxide (NO) synthesis from both constitutive (eNOS) and inducible NO synthase (iNOS). In fact Aspirin, but not other NSAIDs, increases plasma NO [26, 27].

Paul-Clark et al. [28] report the inhibition of acute inflammation by Aspirin depending on induction of plasma NO, which negatively regulates leukocyte–endothelium interaction in the microcirculation. This experiment shows Aspirin was not anti-inflammatory in NOS knock-out mice with IL-1 β -induced peritonitis.

Aspirin and headache

The 1-year period prevalence of migraine in adults has been found around 10%–12%, 6% in men and 15%–18% among women, while 59% of people experiences tension-type headache (TTH) at least 1 day per month [29]. TTH prevalence was related to age, while migraine showed no correlation to it within the studied age interval.

TTH represents the most frequent headache form, involving 82% of headache sufferers, while 14% of this

population is affected by migraine and 4% by a chronic form (chronic daily headache, CDH) [30].

Self-medication constitutes the most common treatment. Among headache sufferers, 91% of TTH patients and 90% of migraine patients use non-narcotic, over-the-counter (OTC) analgesics, which are often taken without any other form of treatment and without consulting a physician [31].

A community-based telephone survey showed that 98% of TTH sufferers depend on OTC medication. At least one dose of this kind of medication was taken, with no difference between males and females. A third of patients was remedicated. Acetaminophen constituted the most used drug (56%), followed by ASA (15%) and ibuprofen (9%) [32]. ASA remains among the most important and well known treatments in headache management [33]. However, the time of administration remains a point of debate.

The common strategy employed for migraine attacks is prompt treatment [34]. Triptans, drugs like NSAIDs and ergotamine respond to this strategy [35]. In the early treatment of migraine, OTC medications are largely used as they do not require a medical prescription and are easily available. A combination of OTC medications (Aspirin 500 mg, acetaminophen 500 mg and caffeine 130 mg) has been compared to a prescription migraine product (sumatriptan 50 mg), underlining a significant efficacy of this association in early migraine abortive treatment [36]. A similar approach has not been investigated yet in TTH, but pain relief as a result of rapid intake seems a reasonable suggestion. In addition, OTC medications have other advantages, such as the absence of cardiovascular contradictions, which are present in triptans. Moreover, OTC drugs could reduce medication costs [37, 38].

On the other hand, Aspirin and other NSAIDs show infrequent limitations. The incidence of upper gastrointestinal tract complications (i.e., bleeding or perforation) in the general population is estimated to be 1–2 cases per 1000 persons/year, with a case fatality rate ranging from 5% to 10%. These results can be found in observational studies involving patients in long-term use of low-dose Aspirin for prevention of cardiovascular diseases [39, 40]. Major and minor bleeding complications can occur as well [41]. Aspirin-induced asthma constitutes another rare but possible immediate adverse event [42].

Aspirin and migraine

The pathophysiological mechanisms of migraine have been analysed in depth [43] and Aspirin represents, in the treatment of acute migraine attacks, a possible therapeutic

choice. Extensive literature exists regarding both its efficacy and safety. Different dosages, formulations and associations with other drugs have been investigated in various randomised, double-blind, placebo-controlled studies.

Compared to placebo, Aspirin was more effective in reducing headache from severe to mild or in achieving pain relief 1 h after administration [44]. A range of ASA dosages between 650 and 1000 mg proved to be considerably more successful for pain reduction than placebo [45]. No statistically significant differences were found between Aspirin and placebo for nausea, vomiting or phonophobia, except in a study conducted by MacGregor et al. [46]. Aspirin's tablet and effervescent versions displayed the same efficacy in this study.

Aspirin is safe and well tolerated. In fact, adverse events of ASA were mild or moderate and similar to placebo responses (8.3% vs. 2.9%) [47]. In the treatment of migraine attacks, 1000 mg effervescent ASA was as effective as 50 mg sumatriptan or 400 mg ibuprofen and all these treatments were superior to placebo ($p < 0.0001$). However, sumatriptan was more effective than ASA in the pain-free response 2 h after administration [48].

Aspirin (650 mg) combined with metoclopramide (10 mg), a dopamine antagonist producing a direct effect on the gastrointestinal tract, proved to be as functional as Aspirin alone. Both were more effective than placebo. No significant differences were found with regard to anti-nausea effects [49, 50].

The efficacy of Aspirin (1000 mg) and a combination of acetaminophen 400 mg and codeine 25 mg showed not significant differences in their activity [51]. At last, a possible role for a low dosage of Aspirin has been suggested in migraine prophylaxis [52].

Aspirin and tension-type headache

The pathophysiological mechanism of TTH has been well investigated, but with little definitive evidence regarding its acute treatments. This is mainly due to the paucity of existing targets in its putative pathophysiological cascade [53, 54]. In the past, peripheral factors have been considered to be leading factors. In a study comparing a group of patients affected by TTH with a healthy control group, Langemark and Olesen observed an increase in tenderness inside the pericranial muscles [55]. It is not clear if muscle factors, although important, represent a cause or an effect of pain, as they could be involved in the development of central sensitisation through the input from myofascial nociceptors [56]. The sensitisation of peripheral nociceptors is explained by the increased pain response in patients affected by episodic TTH. In an experimental human

model of myofascial pain, the infusion of a combination of bradykinin (BK), serotonin [5-hydroxytryptamine (5-HT)], histamine (His) and prostaglandin E2 (PGE2) into the trapezius muscle induces prolonged pain in both patients and controls. Furthermore, patients report a pronounced sensitivity to pain, possibly indicating a peripheral increased excitability or sensitisation in patients with episodic tension headache [57].

Besides, the excitability reduction of brain stem interneurons in TTH patients suggests the possible deficient endogenous pain control mechanisms by recording the blink reflex recovery cycle and the exteroceptive suppression of temporalis muscle activity [58].

At present, central factors apparently play a central role in TTH, principally in chronic forms [59]. According to this hypothesis, the central sensitisation at the spinal dorsal horn/trigeminal nucleus level is given by prolonged nociceptive input from pericranial myofascial tissues. This nociceptive input may result in a secondary sensitisation of supraspinal neurons [60].

Aspirin is useful for acute pain-relief therapy because it is inexpensive, easily available and does not require a medical prescription. Unlike other treatments, a small number of randomised, double-blind, placebo-controlled studies have been carried out. However they demonstrate Aspirin's efficacy in TTH.

Steiner et al. [61] display the statistical difference in terms of efficacy of Aspirin 1000 mg (75.7%; response rate; $p=0.0009$) and 500 mg (70.3%; $p=0.011$) compared to placebo (54.5%).

In this study paracetamol 1000 mg (71.2%; $p=0.007$) results are generally similar to those of Aspirin 500 mg, unlike paracetamol 500 mg (63.8%; $p=0.104$), which proved to be not statistically different from placebo. Differences between Aspirin 1000 mg and placebo were significant ($p\leq 0.022$) after the first 30 min.

Aspirin's adverse events involved 3.9%–7.2% of subjects, 4.5%–5.7% for paracetamol and 1.8% for placebo, not considering dose correlation in the latter two drugs. However all events were mild and transient.

Aspirin's effectiveness compared to placebo has also been demonstrated by Peters et al. [62]. The same results can be also found in a double-blind, placebo-controlled study by Langemark and Olesen. In this study, ASA, in both solid and effervescent forms, was tested, but no statistical difference could be observed [63].

Aspirin's new formulation

Headache therapy and the role of Aspirin have not been sufficiently investigated. However, acute attack thera-

py must converge on high efficacy and fast onset of action.

At present, a new Aspirin formulation with a faster bioavailability is making its debut. The new Aspirin is composed of dry granules containing 500 mg of ASA. This new formulation is moderately effervescent and mouth dispersible after administration onto the tongue, without water. This administration pathway permits a more rapid passage through the stomach to the small bowel (main site of ASA adsorption).

Mouth dispersion does not damage the dental enamel. Reduced exposure (max. 30 s) does not cause erosion of the dental surface.

In a randomised, not blinded, cross-over study, Latta et al. [64] demonstrated the faster onset of action of this new formulation with respect to standard ASA tablets. Maximal ASA plasma concentrations are higher with respect to plain Aspirin tablets (Fig. 1). In this study, the value of C_{max} (maximal plasmatic concentration) of ASA granules is about 50% higher compared to ASA plain tablets (Table 1). Also, the highest concentration is reached already after 20 min, while the standard formulation takes 30 min (Fig. 1).

ASA's relative bioavailability was found to be 118 (CI 1.03–1.34), significantly higher than plain tablets. A similar analysis is also possible for salicylic acid, the principal metabolite of ASA (Fig. 2). Adverse events are similar in both treatments.

In conclusion, the new formulation's rapidity of action could represent a choice for prompt treatment of TTH, especially concerning episodic attacks. The use of Aspirin at the beginning of attacks could be a possible pain-relief treatment, which should be investigated in larger studies.

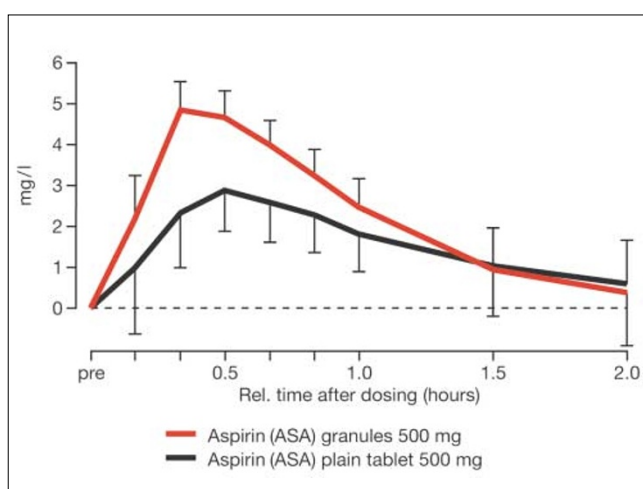


Fig. 1 Plasma concentration vs. time curves for ASA (geometric mean including 1 SD range)

Table 1 Geometric means/geometric standard deviations of ASA pharmacokinetic characteristics in plasma following a single dose administration of two ASA formulations

Parameter	Unit	Granules 500 mg (test)	Plain tablet 500 mg (reference)
C_{\max}	mg/L	5.34/1.27	3.63/1.94
$C_{\max, \text{norm}}$	kg/L	0.85/1.24	0.58/1.92
$t_{\max}^{\#}$	h	0.33 (0.33–1.0)	0.50 (0.33–2.0)
AUC	mg*h/L	4.97/1.19	4.25/1.53
AUC_{norm}	kg*h/L	0.79/1.18	0.68/1.51
MRT	h	0.80/1.26	1.11/1.56
f_{rel}	%	118 (90% CI: 1.03–1.34)	100
$t_{1/2}$	h	0.35/1.16	0.51/1.72

[#] Median (range)

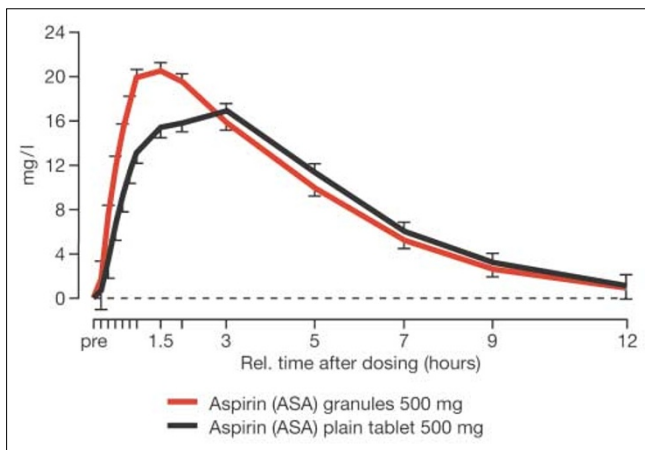


Fig. 2 Plasma concentration vs. time curves for SA (geometric mean including 1 SD range)

Conclusions

The literature concerning Aspirin in the treatment of TTH is not totally satisfying, while more information exists concerning acute migraine treatment. Considering the large population affected by episodic TTH [65], a treatment that is rapid, effective, low-cost and does not require a medical prescription may constitute a binding choice. In such cases, effectiveness and a rapid pain-relief action become essential. Therefore, Aspirin could represent a useful treatment option in TTH, as already shown in acute migraine attack.

The definitive understanding of the pathophysiological mechanics of TTH will offer, in the near future, the basis for new therapeutic opportunities. At present, more studies dealing with this topic are necessary.

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